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(54) Method for the suppression of visceral pain by regulating T-type calcium channel

(57) The disclosure concerns a method for the suppression of visceral pain by regulating the T-type calcium channel; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels. Particularly, the present invention relates to a method for the suppression of visceral pain by regulating an alpha 1G T-type calcium channel in the central nervous system and alpha 1H and alpha 1I T-type calcium channels in the peripheral nervous system; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels. The method of the present invention can be effectively used to suppress visceral pain by regulating T-type calcium channel in a precise mechanism without any side effects.

EP 1 312 362 A1

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a method for the suppression of visceral pain by regulating the T-type calcium channel; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels. Particularly, the present invention relates to a method for the suppression of visceral pain by regulating an alpha 1G T-type calcium channel in the central nervous system and alpha 1H and alpha 1I T-type calcium channels in the peripheral nervous system; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels.

BACKGROUND OF THE INVENTION

[0002] Visceral pain is usually caused by excessive dilation of internal organs, necrosis of these cells or intensive contraction or acute relaxation of internal organs. When there is a tumor, infection or congestion in internal organs, slight mechanical stimulus, acidic or basic solution might cause severe pain. Visceral pain caused especially by tumors cannot be easily suppressed even with an excessive amount of morphine, so neuro-surgical operations such as partial myelotomy of the spinal cord are frequently used (Gybels, *Pain Headache,* 1989, 11:1-402). However, the bilateral cordotomies or commissural myelotomies of spinothalamic tract have many side effects. Relatively, the midline myelotomy that severs the upper middle part of the T10 spinal cord is known as an effective remedy (Nauta, *J. Neurosurg.,* 1997, 86:538-542).

[0003] The above result proves that the visceral pain signal is delivered to the brain through the spinal cord, which supports the fact that the visceral pain signal is delivered through a different channel from other pains. According to a MRI test carried out on a-visceral-pain-induced monkey, it can be known that visceral pain induces the activation of thalamus (Willis, *Proc. Natl. Acad. Sci. USA.*, 1999, 96:7675-79). The result of the test, after all, tells that the visceral pain is delivered from the pain sensory cells in the end of the internal organs through the spinal cord to thalamus. Particularly, thalamus is known as an important sensory processing organ since it delivers the stimulus to the cerebral cortex (McCormick, *Curr. Opin. Neurobiol.,* 1994, 4:550-556).

[0004] The calcium in nerve cells plays an important role in delivering signals between nerve cells. Calcium has many different delivery paths, however, when delivering peripheral stimuli, the voltage-activated calcium channel is crucial. The voltage-activated calcium channel can be categorized into the high voltage-activated calcium channel (HVA) that is activated at a higher voltage than the resting membrane potential and the low voltage-activated calcium channel (LVA) that is activated at a lower voltage. The HVA calcium channel can be subdivided into L, P/Q, N or R-type depending on the pharmacological property of the current, and the LVA calcium channel is differentiated as T-type (Tsien, *Trends Neurosci.,* 1988, 11:431-438).

[0005] The HVA calcium channel is evenly expressed from the peripheral sensory cells to the central nervous system, and is well known to play an important role in transmission of the sense of pain and reflection. The inhibitors against these channels are already commercially available as various anodynes (Schaible, *Prog. Brain Res.,* 2000, 129:173-190). However, it is not yet clearly understood how the LVA calcium channel that generates the T-type calcium current can regulate pain. The reason why the T-type calcium current is categorized as one of the functions of the LVA calcium channel is that when the excitability of nerve cells lowers, the calcium current are generated so that the excitability increases again (Llinas, *J. Physiol (Lond)*, 1981, 315:549-567; McCormick, *Neuroscience*, 1990, 39:103-113). Thus, the nerve cells excited by the T-type calcium channel have the property of burst firings and induce a type of excitability different from tonic firings (Llinas, *J. Physiol (Lond)*, 1981, 315:549-567). The channel protein of the T-type calcium channel is encoded by three different genes, which are referred to as alpha1G, alpha1H and alpha1I respectively (Perez-Reyes, *Nature,* 1998, 391: 896-900). It is known that the alpha1G and alpha1H T-type calcium channels are expressed in the back of the spinal cord, and that the alpha1G is expressed in thalamocortical relay neurons (Talley, *J. Neurosci.,* 1999, 19:1895-1911), and that is identical with the delivery path of the visceral pain. Recently, it has been proved in an experiment using a T-type calcium current inhibitor, mibefradil, that the function of the T-type calcium current in the peripheral nerves is related to hyperalgesic reaction against thermo-stimuli or mechanical stimuli by reducing agents (Todorovic, *Neuron*, 2001, 31:75-85), however, it has not yet been found which T-type calcium channel is related. Mibefradil (RO40-5967) was initially known for lowering blood pressure (Clozel, *Cardiovasc Drugs Ther.,* 1990, 4:731-736; Hefti, *Arzneimittelforschung,* 1990, 40:417-421), and was reported to have a suppression effect (Viana, *Cell Calcium,* 1997, 22: 299-311). Recently, it has been reported that Mibefradil has the most selective suppression effect on T-type calcium channels.

[0006] Thus, the present inventors have studied about visceral pain with alpha1G-/- transgenic mice and found that the alpha1G-/- transgenic mice show hyperalgesia to visceral pain caused by acetic acid. In wild-type mice, visceral pain caused by acetic acid could be alleviated by administration of mibefradil at the periphery but enhanced when mibefradil is injected in the brain. The present invention has been accomplished by

confirming that visceral pain can be modulated by controlling the T-type calcium channel.

SUMMARY OF THE INVENTION

[0007] It is an object of the present invention to provide a method for the suppression of visceral pain by regulating the T-type calcium channel.

[0008] It is another object of the present invention to provide a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient.

[0009] It is a further object of the present invention to provide a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels.

[0010] In a further object of the present invention, there is provided a tetraline T-type calcium channel inhibitor for use in the suppression of visceral pain.

[0011] In a further object of the present invention, there is provided the use of a tetraline T-type calcium channel inhibitor in the manufacture of a medicament for use in a method of suppressing visceral pain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

FIG. 1 is a graph showing the responses of alpha 1G-/- mice and normal mice against mechanical stimuli such as paw withdrawal and tail flick test,
●: normal mice ○: alpha 1G-/- mice

FIG. 2 is a graph showing the responses of alpha 1G-/- mice and normal mice against thermostimulus Hyperalgesia that is caused by a thermostimulus by radiation or by inflammation,
■: normal mice □: alpha 1G-/- mice

FIG. 3 is a graph showing the responses of alpha 1G-/- mice and normal mice against pain in internal organs that is caused by acetic acid,
●: normal mice ○: alpha 1G-/- mice

FIG. 4 is a graph showing the suppression degree in accordance with the concentration of a T-type calcium channel inhibitor, mibefradil.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0013] The present invention provides a method for the suppression of visceral pain by regulating the T-type calcium channel.

[0014] The present invention also provides a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient.

[0015] The present invention also provides a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels.

[0016] Hereinafter, the present invention is described in detail.

[0017] The present invention provides a method for the suppression of visceral pain by regulating the T-type calcium channel.

[0018] The present invention provides a method for the suppression of visceral pain either by activating alpha 1G T-type calcium channel function in the brain or by suppressing alpha 1H and alpha 1I T-type calcium channel function in the peripheral nervous system.

[0019] The T-type calcium channel is categorized into alpha 1G, alpha 1H and alpha 1I depending on the organization unit of small-pore forming, and in the present invention, the inventors carried out an experiment related to pain by using the alpha 1G-/transgenic mice so as to suppress the function of the alpha 1G protein, one of the component of alpha 1G T-type calcium channel. It has been known that mechanical stimuli, which are acute pains, are controlled by spinal reflex, and the responsiveness of the mechanical stimuli is proportionate with the intensity of the pains received by the peripheral organs. The alpha 1G-/- mice do not have much difference from the normal mice in the paw withdrawal and tail flick test (see FIG. 1). In addition, the result of the thermal pain response analysis using radiant heat in which spinal reflex and supraspinal mechanism is involved shows that the alpha 1G-/- mice does not have much difference from the normal mice, either in thermo-stimulus hyperalgesia caused by inflammation reaction or thermo-stimulus by infrared radiation (see FIG. 2). As mentioned above, deducing from the fact that the alpha 1G-/- mice reacts normally to thermal or mechanical stimuli, it can be known that the loss of the alpha 1G T-type calcium channel do not affect the development of the peripheral sensory organs, that is, the nerves that are involved in spinal reflection and inflammation reaction.

[0020] From the observation of the response of the internal pains induced by acetic acid, the alpha 1G-/- mice show serious hyperalgesia to the visceral pain induced by acetic acid (see FIG. 3). It shows that the alpha 1G T-type calcium channel is selectively involved in the control of visceral pain. In order to find out whether the alpha 1G T-type calcium channel that is involved in visceral pain control functions in the peripheral sensory organs or in the part where the spine is connected to the brain and thalamus, the present inventors injected mibefradil, a T-type inhibitor, in the same spot of acetic acid injection. The result was that there was analgesia to the visceral pain caused by the acetic acid (see FIG. 4). Mibefradil in this case suppresses the T-type calcium channel only in the peripheral nervous system since it cannot pass through the brain barrier inside the body.

[0021] From the result, it can be deduced that the pain suppression of the alpha 1G T-type calcium channel only functions in the central nervous system, not in the peripheral nervous system. It can also be known that the

other types of the T-type calcium channels, alpha 1H and alpha 1I calcium channels increase pain in the peripheral nervous system.

[0022] As described above, the T-type calcium channel functions wholly differently in the peripheral nervous system and in the central nervous system concerning visceral pain control, and the T-type calcium channel is activated when the resting membrane potential lowers, thus suppressing the membrane potential from being low, which increase the activity of the visceral pain sensory cells in the peripheral organs. This is supported by the fact that the T-type calcium channel functions against hyperalgesia to mechanical or thermal stimuli induced by reducing agents. As for visceral pain, the dilation of intestinal cells or outflow of reduced substrates from cells caused by necrosis is brought along, so it is highly likely that hyperalgesia is already included in the normal algesia.

[0023] The present invention also provides a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient.

[0024] When a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient is injected into a body, the inhibitor reacts with alpha 1H and alpha 1I T-type calcium channel, which will eventually suppress visceral pain by suppressing the functions of the above-mentioned alpha 1H and alpha 1I T-type calcium channel.

[0025] In the present invention, the T-type calcium channel inhibitor is selected from a group consisting of mibefradil and Ni^{2+}.

[0026] Moreover, the present invention provides a method of screening a visceral pain inhibitor by investigating the suppression activation of the T-type calcium channel.

[0027] In the present invention, the suppression activity of the T-type calcium channel of chemical materials or natural materials is investigated; the materials that have suppression activity to the T-type calcium channel are selected; and among the selected materials, the material that has an analegesic effect only on the visceral pain induced by acetic acid, et al. is found by carrying out experiments related pain with alpha 1G-/- mice and normal mice.

[0028] In accordance with the present invention, the T-type calcium channel inhibitor has a suppression effect on visceral pain in a precise mechanism without any side effects, therefore, the selected material from these T-type calcium channel inhibitors can be used as a visceral pain inhibitor.

EXAMPLES

[0029] Practical and presently preferred embodiments of the present invention are illustrative as shown in the following Examples.

[0030] However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

Example 1: Generation and management of alpha 1G-/- transgenic mice

<1-1> Generation of alpha 1G -/- transgenic mice

[0031] The present inventors have produced transgenic mice that have the genotype of alpha 1G-/- by using an embryo that has the genotype of alpha 1G+/(International Depository Authority: Korea Institute of Bioscience and Biotechnology Gene Bank, Accession No: KCTC 10086 BP). Particularly, the heterozygote transgenic mice having alpha 1G-/- genotype was produced by transplanting the embryo having alpha 1G+/- genotype to a surrogate mother, and the homozygote transgenic mice having alpha 1G-/- genotype was produced by crossbreeding male and female of the above heterozygote transgenic mice.

<1-2> Management of animal

[0032] All animals were allowed to access freely to food and water under the environment of controlled temperature and humidity, and they were bred under the condition in which the daytime starts at 8 o'clock in a 12 hour cycle of daytime and nighttime. All male and female F2 mice were used in the experiments when they are 8~15 week old.

Example 2: Analysis of the response to mechanical stimuli

[0033] In order to observe the response of the alpha 1G-/- mice to mechanical stimuli, the present inventors carried out a paw withdrawal test and a tail flick test.

<2-1> Paw withdrawal test

[0034] Paw withdrawal test was based on that described by Mogil et al (Mogil et al., *J. Neurosci.*, 1999, 19:RC25). Particularly, the alpha 1G -/- mice were placed individually on a fine mesh metal floor and allowed to acclimate for at least 2 hr. The mechanical threshold was measured using calibrated *von Frey* filaments (Stoelting) and was defined as the bending force, in grams, at which the mice withdraws its paw. The filament was applied from underneath the floor, through the mesh, to the plantar surface of the paw for each limb. The response score was assessed as the total numbers of paw withdrawals in 10 consecutive trials for each filament and the average value of the response was used in the analysis.

<2-2> Tail flick test

[0035] The local pressure required to elicit tail flick

was determined using *von Frey* filaments. The alpha 1G -/- mice were habituated in the mice restrainer 30 minutes every day for 2 weeks. The bending force of each monofilament was applied locally to the tail resting on a table. Only flicking of the pressed tail was defined as a nociceptive response. The response score was assessed as the average of the total tail flicking number in 10 consecutive trials with an interval of 10 min between each filament application.

[0036] As a result, the alpha 1G -/- mice do not have any difference from the normal mice in responding to thermal or mechanical stimuli using *von Frey* (FIG. 1)

Example 3: Responses to radiant heat and hot plate

[0037] The present inventors examined the thermal pain response by using radiant heat assay (Hargreaves test) wherein the mechanism of spinal reflex and supraspine is involved.

<3-1> Paw withdrawal test

[0038] The present inventors measured hind-paw withdrawal latency by Hargreaves' method (Hargreaves et al., *Pain,* 1988, 32:77-88) using an Ugo Basile plantar test apparatus (Stoelting). Mice were placed in a Plexiglas box on an elevated glass plate and acclimated for 2 hr before testing. The tests were performed at low (20) and high (40) intensities. Response was defined as withdrawal of a paw when head turning and paw licking were observed. The time was defined as the paw withdrawal latency. Five to ten minutes were allowed between each trial on both hind-paws and 4 to 5 trials were averaged for each mice.

<3-2> Hot plate test

[0039] Thermal pain response was assessed using the hot-plate test (Mogil et al., *J. Neurosci.*, 1999, 19: RC25). For the hot-plate test, the mice was habituated for 2 days in a transparent testing box (14 X 14 X 20 cm) with a metal bottom. The mice was then placed on the box pre-heated to the desired temperature in a thermoregulated water bath, and the time was recorded to the first hind-paw licking or jumping response (cut-off time, 60 s).

[0040] As a result, the alpha 1G -/- mice did not have much difference from the normal mice in the response to thermal hyperalgesia caused by inflammation reaction or thermostimuli by infrared radiation (FIG. 2). Thus, it was confirmed that the loss of the alpha 1G T-type calcium channel did not affect the development of the peripheral sensory organs, that is, the nerves that are involved in spinal reflection and inflammation reaction.

Example 4: Analysis of visceral pain induced by acetic acid (Writhing test)

[0041] The present inventors injected 0.6% acetic acid into the peritoneal cavity of mice to examine the acetic acid-induced visceral pain response. The visceral pain is elicited secondarily to a delayed inflammatory response and induced abdominal stretching and writhing behavior (Gyires and Torma, *Arch Int. Pharmacodyn. Ther.*, 1984, 267:131-140). Mice were placed individually in a transparent home cage (24 X 18 X 12 cm) and allowed to acclimate for at least 60 min. Then, 0.6% acetic acid (5.0 mg/kg) was injected into the peritoneum, after which the mice was returned to the testing chamber. The number of abdominal stretches or writhing motions was counted for 20 min. All mice were used only once in this experiment.

[0042] As a result, the alpha 1G -/- mice showed severe hyperalgesia to the visceral pain induced by acetic acid (FIG. 3), which means that the alpha 1G T-type calcium channel is involved selectively in controlling the sense of visceral pain.

Example 5: Analysis of visceral pain induced by mibefradil

[0043] In order to find where the alpha 1G T-type calcium channel functions in relation to controlling visceral pain, whether the peripheral nerves or the part where the spine was connected to thalamus and brain, the T-type inhibitor, mibefradil, was injected into peritoneum, the same spot where the acetic acid (the visceral pain inducer for the normal mice) was injected.

[0044] Particularly, in order to find out how mibefradil, the T-type calcium channel inhibitor functions, mibefreail was dissolved in 0.9% of NaCl at the concentration of 5 mg/ml. The degree of writhing was measured in a visceral pain inducing experiment 20 minutes after the injection of the said mibefradil at the concentration of 1, 10 and 30 mg/kg respectively in peritoneum of the mice.

[0045] As a result, the mibefradil induced analgesia to the visceral pain caused by acetic acid in the normal mice (FIG. 4).

INDUSTRIAL APPLICABILITY

[0046] As shown above, a method of the present invention can be effectively used to suppress visceral pain by regulating T-type calcium channel in a precise mechanism without any side effects.

[0047] Those skilled in the art will appreciate that the concepts and specific embodiments disclosed in the foregoing description may be readily utilized as a basis for modifying or designing other embodiments for carrying out the same purposes of the present invention. Those skilled in the art will also appreciate that such equivalent embodiments do not depart from the spirit and scope of the invention as set forth in the appended

claims.

Claims

1. A method for the suppression of visceral pain by regulating the T-type calcium channel.

2. The method as set forth in claim 1, wherein the T-type calcium channel is selected from a group consisting of alpha 1G, alpha 1H and alpha 1I T-type calcium channels.

3. The method as set forth in claim 1, wherein the suppression of visceral pain is achieved by activating the function of alpha 1G T-type calcium channel in the central nervous system.

4. The method as set forth in claim 1, wherein the suppression of visceral pain is achieved by inhibiting the function of alpha 1H and alpha 1I T-type calcium channels in the peripheral nervous system.

5. A visceral pain inhibitor containing the T-type calcium channel inhibitor as an effective ingredient.

6. The visceral pain inhibitor as set forth in claim 5, wherein the T-type calcium channel is alpha 1H or alpha 1I T-type calcium channel.

7. The visceral pain inhibitor as set forth in claim 5, wherein the T-type calcium channel inhibitor is selected from a group consisting of mibefradil and Ni^{2+}.

8. A screening method of the visceral pain inhibitor by investigating the suppression activity of the T-type calcium channel.

9. A tetraline T-type calcium channel inhibitor for use in the suppression of visceral pain.

10. The use of a tetraline T-type calcium channel inhibitor in the manufacture of a medicament for use in a method of suppressing visceral pain.

FIG. 1

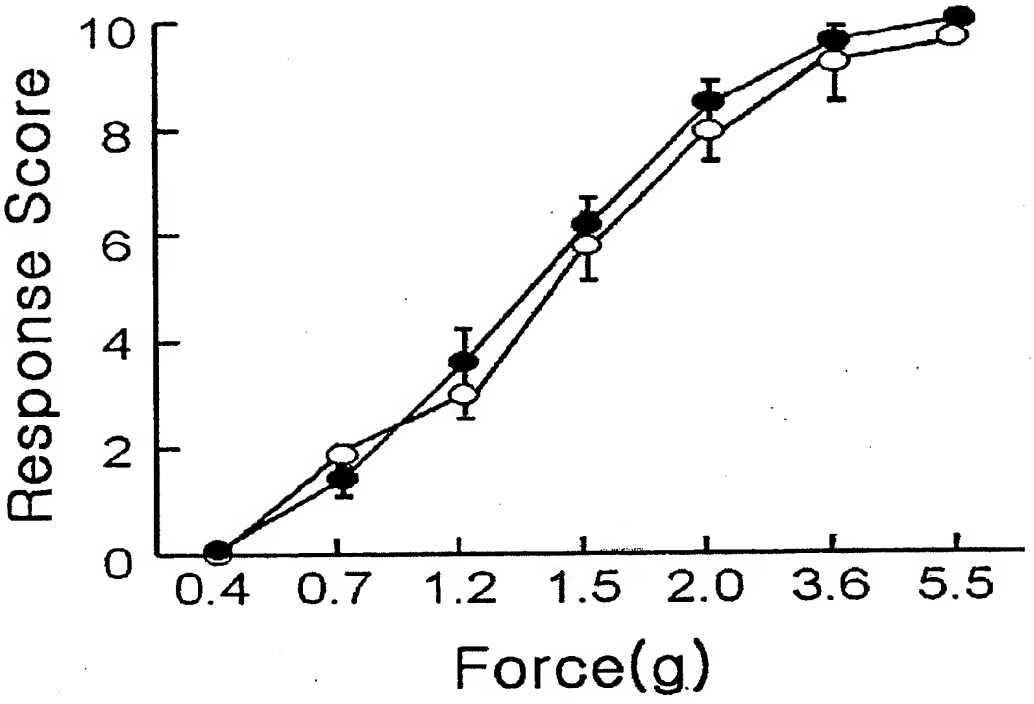


FIG. 2

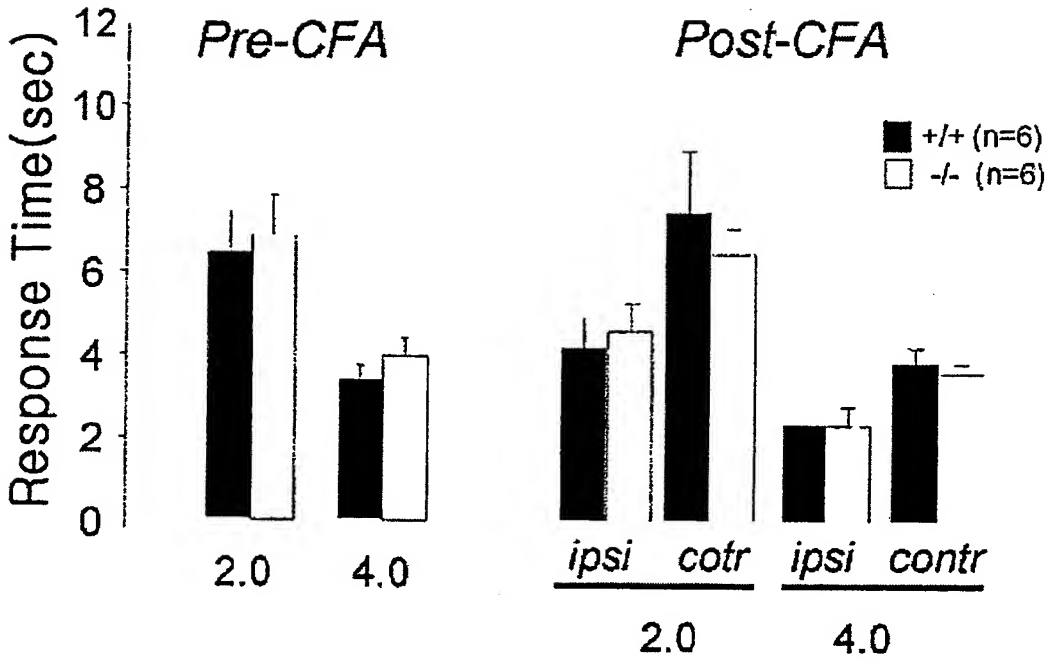


FIG. 3

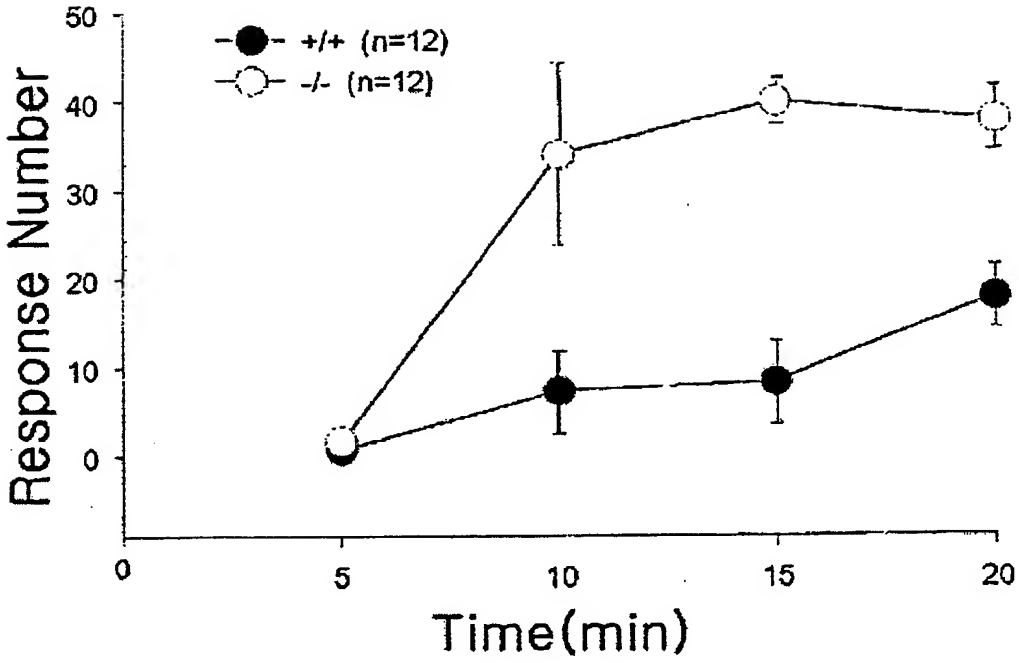
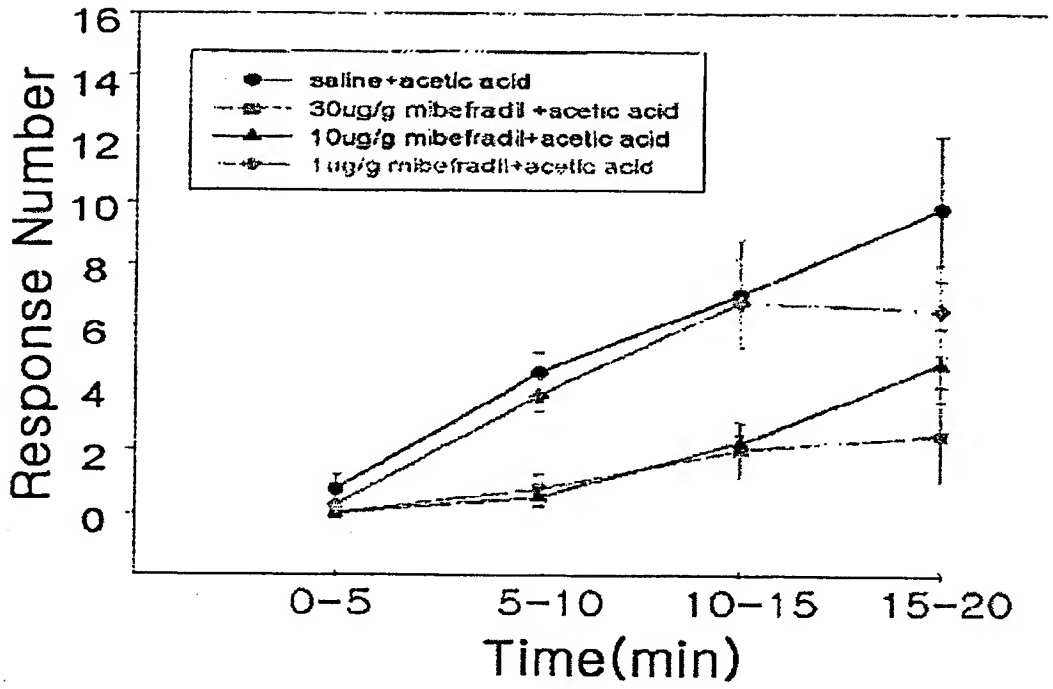


FIG. 4



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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 02 25 7625

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	EP 1 031 350 A (WARNER LAMBERT CO) 30 August 2000 (2000-08-30) * page 2 * * page 3, line 29-31 * * page 5 * * page 6 * ---	1-6	A61K31/4184 A61K31/00 A61K33/00 A61P25/00 A61P43/00
X	WO 95 33723 A (SMITHKLINE BEECHAM PLC ;BROWN THOMAS HENRY (GB); COOPER DAVID GWYN) 14 December 1995 (1995-12-14) * page 8, line 22-31 * * page 9, line 4 * ---	1-6	
Y	WO 01 30844 A (ORTHO MCNEIL PHARM INC) 3 May 2001 (2001-05-03) * page 6 - page 7 * * page 8 - page 9 * * page 52 - page 53 * --- -/--	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	26 March 2003	Domingues, H

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

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INCOMPLETE SEARCH
SHEET C

Application Number
EP 02 25 7625

Although claims 1-4 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched incompletely:
1-6 and 8-10

Reason for the limitation of the search:

Present claims 1-6, and 8-10 relate to compounds defined by reference to a desirable biological property (the regulation of T-type calcium channel), leading to a lack of clarity within the meaning of Art. 84 EPC. The application provides support within the meaning of Art. 84 EPC and disclosure within the meaning of Art. 83 EPC for only a very limited number of such compounds. In view of this, the claims so lack clarity and support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Therefore, the search has been carried out for those parts of the application which do appear to be clear, namely for those compounds recited in the examples and in claim 7 (Ni^{2+} and mibefradil) and for the term "visceral pain inhibitor" per se.
Attention is also drawn to the fact that it may well be the case that compounds are known to suppress visceral pain but have not been described as T-type calcium channel inhibitors.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 7625

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	WO 99 28342 A (SIBIA NEUROSCIENCES INC ;WILLIAMS MARK (US); HANS MICHAEL (US); HA) 10 June 1999 (1999-06-10) * page 8 * * page 26 * * page 44 * * example 3 * * page 95 - page 97 * * page 100 - page 101 * * page 62 * * page 70 * ---	1-10	
X	US 5 773 463 A (HARLING JOHN DAVID ET AL) 30 June 1998 (1998-06-30) * column 1, line 47-50 * * column 8, line 47-67 * ---	5,6,9,10	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
Y	WO 00 12110 A (HEATON JEREMY P W ;UNIV KINGSTON (CA); ADAMS MICHAEL A (CA)) 9 March 2000 (2000-03-09) * page 10, line 3-7 * ---	5-10	
A	ANGUS J A ET AL: "Targetting voltage-gated calcium channels in cardiovascular therapy" LANCET, vol. 356, no. 9238, 14 October 2000 (2000-10-14), pages 1287-1289, XP004264172 ISSN: 0140-6736 * the whole document * ---	1-10	
	-/--		

EPO FORM 1503 03.82 (P04C10)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 7625

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	MUTH J N ET AL: "Use of transgenic mice to study voltage-dependent Cachannels" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 22, no. 10, 1 October 2001 (2001-10-01), pages 526-532, XP004307622 ISSN: 0165-6147 * the whole document *	1-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

Application Number
EP 02 25 7625

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☒ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 02 25 7625

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-7, 9 and 10

   A method for the suppression of visceral pain by regulating T-type calcium channels;visceral pain inhibitors, particularly mibefradil, Ni2+ and tetraline compounds that are T-type calcium channel inhibitors; the use of tetraline compounds that are T-type calcium channel inhibitors for the treatment of viscreal pain.

2. Claim : 8

   A screening method of visceral pain inhibitors by investigating the suppression activity of the T-type calcium channel.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 7625

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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26-03-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1031350 A	30-08-2000	EP 1031350 A1	30-08-2000
		AU 2909800 A	14-09-2000
		BR 0008323 A	29-01-2002
		CA 2360528 A1	31-08-2000
		CN 1341018 T	20-03-2002
		CZ 20012982 A3	15-05-2002
		WO 0050027 A1	31-08-2000
		EP 1154768 A1	21-11-2001
		HU 0200344 A2	29-05-2002
		JP 2002537332 A	05-11-2002
		NO 20014046 A	20-08-2001
WO 9533723 A	14-12-1995	WO 9533723 A1	14-12-1995
		EP 0763022 A1	19-03-1997
		JP 10500698 T	20-01-1998
WO 0130844 A	03-05-2001	US 6358706 B1	19-03-2002
		AU 7871600 A	08-05-2001
		EP 1224218 A1	24-07-2002
		TR 200201119 T2	21-11-2002
		WO 0130844 A1	03-05-2001
WO 9928342 A	10-06-1999	US 6528630 B1	04-03-2003
		AU 1802699 A	16-06-1999
		CA 2312195 A1	10-06-1999
		EP 1042468 A2	11-10-2000
		JP 2001525161 T	11-12-2001
		WO 9928342 A2	10-06-1999
US 5773463 A	30-06-1998	AU 7532094 A	28-02-1995
		EP 0711272 A1	15-05-1996
		JP 9500879 T	28-01-1997
		WO 9504028 A1	09-02-1995
		ZA 9405504 A	26-01-1996
WO 0012110 A	09-03-2000	AU 5403499 A	21-03-2000
		CA 2340206 A1	09-03-2000
		WO 0012110 A2	09-03-2000
		EP 1235563 A2	04-09-2002
		US 2003008020 A1	09-01-2003
		US 6284763 B1	04-09-2001
		US 2002035067 A1	21-03-2002

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82